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High Throughput Drug Screening

Principal Investigator: DAWSON, TED M
Grant Number: 2P50NS038377-06A1
Title: Parkinson's Disease Research Center of Excellence

Abstract: The overall goals of this proposal are to understand the role of alpha-synuclein, parkin, DJ-1 and synphilin-1 in the pathogenesis and pathology of Parkinson's disease (PD) and to define the molecular mechanisms of neuronal injury in animal models of PD. The program represents a multi-disciplinary, mechanistic approach involving interactive, productive investigators with complementary areas of expertise who have long been committed to the studies of neurodegenerative diseases. Their aim will be to integrate the activities of various disciplines such that the interrelationships will result in a greater scientific contributions and achievements if each project were pursued individually. The program has one major theme: To understand the role of familial associated genes alpha-synuclein, parkin and DJ-1 in the pathogenesis of Parkinson's disease and related disorders. The role of alpha-synuclein, parkin, DJ-1 and synphilin- 1 in PD pathogenesis will be investigated using molecular, transgenic, neuropathologic, cell biologic and neurobehavioral approaches to examine the mechanism of neuronal dysfunction and injury clue to alterations in these gene products. The mechanism of neuronal loss in Parkin knockout mice and alpha-synuclein A53T transgenic mice will be characterized. We will determine whether parkin interacts with alpha-synuclein and further explore the relation between and parkin, alpha-synuclein and synphilin-1. We will explore alpha-synuclein processing and modifications and the relationship of synphilin-1 to alpha-synuclein. Furthermore, we will investigate the potential function of DJ-1 and it role in PD Pathogenesis. We believe that our multi-disciplinary approach has the capacity to produce unique information concerning the mechanisms of neurodegeneration in genetic animal models of Parkinson's disease and the related synucleinopathies and to lead to better understanding of the function and the role of alpha-synuclein, parkin, DJ-1 and synphilin-1 in normal and pathophysiologic processes related to PD. The program consists of four projects: 1) Mouse Models of Parkin Biology and Pathobiology 2) PD Cell Models: Alpha-synuclein and Interacting Proteins; 3) Mechanisms of Neurodegeneration in Human Alpha-synuclein Transgenic Mice; 4) The Role of DJ-1 in Parkinson's Disease and four cores A) Administration and Training; B) Transgenic and Neurobehavior; C) Neuropathology and D) Clinical.-

Principal Investigator: LANSBURY, PETER T
Grant Number: 3P50NS038375-05S1
Title: FAMILIAL PARKINSON'S DISEASE: CLUES TO PATHOGENESIS

Abstract: Unavailable

Principal Investigator: MATTERN, MICHAEL R
Grant Number: 5R43NS047948-02
Title: Screen For Inhibitors of Parkin E3 Autoubiquition

Abstract: Neurodegenerative disease represents a major challenge to the maintenance of health and quality of life in diverse segments of the population. Among the various diseases of this class, Parkinson's disease (PD) is a major cause of morbidity and diminished life expectancy, and there is today an intense effort to discover novel treatments. A promising approach for therapeutic intervention is treatment designed to increase the cellular level of parkin, a protein which has been found to antagonize neurodegeneration in model systems, and which is linked genetically with some forms of PD. The selection and validation of targets that can be manipulated to achieve this effect depends on an increasing amount of information relating to parkin regulation. A novel area for drug discovery -- protein homeostatic regulation via ubiquitin pathway enzymes -- has recently been demonstrated to have relevance to the search for anti-neurodegenerative drugs. Parkin has, in fact, been determined to be a RING-finger E3 ubiquitin ligase that catalyses ubiquitination and, subsequently, induces proteasomal degradation of various proteins associated with neurodegeneration. In addition, it catalyses its own ubiquitination. Thus, selective inhibitors of parkin autoubiquitination are hypothesized to have a neuroprotective effect. In Phase I, it is proposed to establish a yeast-based screening assay for inhibitors of parkin autoubiquitination and a selectivity counter screen for ubiquitination of alpha-synuclein, a parkin substrate. Essential components of the E3 system (parkin) will be cloned and expressed in S. cerevisiae, along with human parkin or alpha-synuclein linked to p53, and a reporter construct that monitors p53 activity (beta-galactosidase activation). The reconstructed E3 ligase function and reporter system will then be configured and validated as a high throughput screen for inhibitors of parkin autoubiquitination. Collections of plant and marine organism extracts and small molecules from the NCI and academic collaborators, will be screened for potent inhibitors of this activity. In Phase II, fractionation of active extracts will be guided by the assay to identify active principles. Novel pure compounds arising from this effort will be considered as development candidates for PD therapy. The modular assay construction format will permit evaluation of other E3s that are associated with a variety of diseases.-

Principal Investigator: PARNG, CHUENLEI
Grant Number: 1R43NS048607-01
Title: In Vivo Screen for Neuroprotective Agents

Abstract: Aberrant apoptosis is implicated in several neurodegenerative disorders including, stroke, brain trauma, spinal cord injury, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's and Huntington's disease. These neurodegenerative diseases are associated with high morbidity and mortality, and treatment options are limited. Agents that modulate apoptosis are a major focus of drug development efforts by biopharmaceutical companies. Assessment of drug effects in a convenient vertebrate model, prior to proceeding to evaluation in complex systems, such as mouse, can potentially streamline drug development and dramatically reduce costs. Zebrafish mutants exhibiting aberrant apoptosis in the central nervous system are an excellent animal model for studying neurodegeneration. Using a zebrafish neurodegenerative mutant line and a vital dye apoptosis assay, this Small Business Innovation Research project proposes to characterize embryogenesis and apoptotic patterning in zebrafish embryos, and to develop a rapid and effective in vivo screen for neuroprotective therapeutics.-

Principal Investigator: PEREZ, RUTH G
Grant Number: 5R21NS045336-02
Title: Cell-based assays for neuroprotection in parkinsonism

Abstract: Unavailable

Principal Investigator: RAPTIS, ANASTASIOS
Grant Number: 5R44NS043948-03
Title: Potential Brain Therapeutics

Abstract: Use of botanical products such as exogenous antioxidants has gained considerable momentum in the last few years in therapy of human degenerative diseases. Among these antioxidants, tumeric, neem, guggul, alpha-tocopherol, Beta-carotene, and ascorbic acid have been shown to have a special relevance in maintaining the redox equilibrium in various cell types, including those of the nervous system. They have a strong commercial potential as dietary supplements or as potential pharmaceutical agents in the treatment of various human degenerative diseases. In Phase I of the project, our aim is to develop cell free in vitro assay systems for the measurement of the biological activities of these compounds, using biological molecules present in their free form as targets of reactive oxygen species (ROS). In the development of these methods, we will take into account the critical factors that may influence the results, for example: (a) different types of ROS; (b) different systems for the generation of these ROS; (c) different molecular targets of ROS, and (d) different methods for the measurements of the molecular lesions produced by the ROS. In Phase II of the proposed project, we will optimize assay systems in which the target molecule is present as an integral part of the cell (intact-cell systems). The intact-cell systems will use functional neurons and astrocytes in which the effects of ROS and antioxidants will be measured by their effects on the structural integrity of the mitochondrial DNA. Also, in Phase II, we will develop an approach for assigning antioxidant indices to mixtures of antioxidants, using a minimum number of different assays. -

Principal Investigator: RODRIGUEZ, ALICE L
Grant Number: 1F32NS049865-01
Title: Development of allosteric potentiators of mGluR4

Abstract: Treatment of Parkinson's disease (PD) has traditionally focused on dopamine replacement strategies such as LDOPA. While generally effective early on, L-DOPA has often proven inadequate for long term treatment due to serious adverse side effects. Recent studies in Dr. Conn's laboratory suggest that activators of metabotropic glutamate receptor mGluR4 may provide a novel pharmacological approach to the treatment of PD by targeting the indirect pathway of the basal ganglia. Furthermore, Dr. Conn and coworkers have developed a novel approach to activation of mGluR4 by development of allosteric potentiators that do not activate this receptor directly but dramatically potentiate the response to glutamate. While these studies provide an exciting proof of principle for a novel approach to activation of mGluR4, there is a need to develop novel compounds that have a higher potency and are useful for further in vivo studies. The goal of this work is to develop novel potent and selective allosteric potentiators of mGluR4. A threefold approach will be implemented, beginning with performing a high throughput screen mining for compounds that potentiate the glutamate response of mGluR4. In parallel with the HTS, medicinal chemistry studies will be pursued to improve upon the properties of known potentiators. Finally, mutagenesis studies will be performed to develop a better understanding of the molecular interactions involved in potentiator binding which will subsequently aid in the design of future compounds. Together these approaches will result in the development of novel small molecules that have a therapeutic effect on PD by reducing transmission through the indirect pathway. Furthermore, these studies will be complemented by ongoing electrophysiology and behavioral studies in Dr. Conn's laboratory that will determine the effects of these compounds in vitro models of basal ganglia function. -

Principal Investigator: SARANG, SATINDER S
Grant Number: 1R43NS050920-01
Title: PESTICIDE-SYNUCLEIN INTERACTIONS AS RISK FACTORS FOR PD

Abstract: Parkinson's disease (PD) and other age-associated neurological disorders represent one of the largest unmet medical needs in developed countries. However, the discovery of improved diagnostics and therapeutics for these disorders is hampered by incomplete understanding of underlying disease mechanisms and risk factors. Oxidative stress, mitochondrial dysfunction, and protein aggregation have been implicated as major mechanisms causing dopaminergic neuronal loss in PD. Epidemiological studies have revealed an association between pesticide exposure and PD, and pesticides that cause oxidative stress and mitochondrial dysfunction, such as rotenone and paraquat, are used in cellular and animal models of PD. Furthermore, interactions between pesticides and the PD-linked gene alpha-synuclein have been postulated. Although almost 1000 pesticide active ingredients are currently marketed, these compounds have not been systematically screened for neurotoxicity in cellular or animal models of PD. The identification of pesticides that interact with alpha-synuclein to cause neurodegeneration may lead to the discovery of novel candidate risk factors and more representative disease models for PD. For this proposal, investigators at Cambria Biosciences will exploit a published moderate-to-high throughput neuronal cell-based model of PD, with the goal of identifying individual pesticides and synergistic pesticide combinations potentially involved in the pathogenesis of PD. Our established cellbased model of PD will be used to screen -approximately 350 registered pesticides to identify neurotoxic pesticides. Our specific aims include: (1a) identifying neurally-active pesticides that induce cell injury to two PD-like cell lines that stably express wild type (WT) human alpha-synuclein and mutant A53T alpha-synuclein; (1b) identifying any synergistic effects of neurotoxic pesticides in inducing cell damage in these a-synuclein-expressing neuronal cells; and (2) characterizing the activity of these neurotoxic pesticides and pesticide combinations using primary mature mesencephalic DA neurons. The identified neurotoxic pesticides will be employed in follow-on Phase II studies for the development of improved in vitro and in vivo PD models, which will ultimately be used to screen for neuroprotective compounds as part of a comprehensive drug discovery program. -

Principal Investigator: YOUNG, ANNE B
Grant Number: 2P50NS038372-06A1
Title: MGH/MIT MORRIS UDALL CENTER OF EXCELLENCE IN PD RESEARCH

Abstract: The MGH/MIT Morris Udall Center of Excellence in PD Research is taking a broad, collaborative and interactive approach to the study of Parkinson's disease. The Projects address critical questions concerning the selective vulnerability of dopamine neurons, the mechanism and consequences of Lewy body formation and alpha-synuclein aggregation, the neural systems consequences of parkinsonism and synuclein pathology, and molecular approaches for modifying this pathology. These issues will be explored using a range of systems, from yeast genetics, to mammalian cell culture, to rodent models to human postmortem material. The Center incorporates state-of-the-art technologies including high throughput yeast genetic screens to identify modifiers of synuclein aggregation and toxicity, viral vector gene transfer to study factors in mammalian cell culture and rodent models, multi-unit tetrode recordings to study striatal plasticity, fluorescence lifetime imaging to study protein-protein interactions, and laser capture microdissection and gene arrays to study transcriptional dysregulation. The Center has a Clinical and Training Core that provides care to patients with Parkinson's disease, gathers data on clinical features of the disease and response to therapy, solicits brain donations for neuropathological study, and trains outstanding clinician scientists to be future leaders in the field. The Center also has a Bioinformatics Core that serves to integrate and analyze data across the projects, and facilitate sharing of the information. The Administrative Core is charged with management of the Center and facilitating the sharing of information, ideas, and reagents among the investigators and with other components of the Udall Centers consortium. The investigators of the MGH/MIT Center are dedicated to a program of collaborative and interactive studies which will lead to better treatments for people with Parkinson's disease.-

Principal Investigator: ZHOU, JIANHUA
Grant Number: 5R21NS045351-02
Title: A cell base system for compounds regulating tau splicing

Abstract: Unavailable

Principal Investigator: ZHOU, JIANHUA

Grant Number: 5R01NS041665-05

Title: SMN associated proteins and compounds for SMA therapy

Abstract: The autosomal recessive spinal muscular atrophy (SMA) is one of the most common genetic causes of infant death. In SMA, there is anterior horn cell death and muscle weakness. Deletions or mutations in the survival motor neuron gene, SMN, are responsible for the disease. There are two SMN genes. However, only telomeric copy (SMNt or SMNI) causes disease. Due to a single nucleotide difference, T in the second gene SMN2 from C in SMNI, the majority of SMN2 mRNA or protein skips exon7, resulting in an unstable SMNA7 protein and reduction of its oligomerization ability. Therefore, the presence of the SMN2 gene in SMA patients can not compensate for the loss of the SMNI gene. To understand the pathogenesis of SMA, the first goal of this proposal is to use the yeast two-hybrid screens to identify SMN interacting proteins, particularly those from motor neurons. The interactions will be further characterized by other complementary methods including mammalian two hybrid assays, in vitro binding assays and in vivo co-immunoprecipitation assays. The biological significance of interactions between SMN and its interactors will be investigated in cell lines, and as long-term goals, in animal models. The second goal of this proposal is to develop cell-based systems for therapeutic studies of SMA based on the hypothesis that increasing of total or full-length SMN protein from SMN2 would reduce the severity of SMA. Stable cell lines and transgenic mice expressing exon 7 splicing cassettes with reporters such as GFP, luciferase or P-lactamase will be established. Both high and low throughput screening (HTS, LTS) will be used to identify small molecules to promote inclusion of exon 7 in SMN2 mRNA and protein. These compounds will be tested in SMA mouse models. Signal pathways and other mechanisms that regulate RNA splicing of SMN genes will be investigated. 1 ZNS1 SRB R(01) 3 1 R01 NS41665-01 DECEMBER 13-14, 2000 ZHOU, DR. JIANHUA -